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Testing the inter-hemispheric competition account of visual extinction with combined TMS/fMRI

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ABSTRACT

Theoretical models of visual neglect and extinction entail claims about the normal functioning of attention and parietal cortex in the healthy brain: (1) 'pseudoneglect', a commonly observed attentional bias towards left space, reflects the greater dominance of parietal cortex activity of the right versus left hemisphere; (2) the capacity to distribute attention bilaterally depends causally on the relative balance of parietal activity between the hemispheres; (3) disruption of the dominant right parietal cortex shifts this inter-hemispheric balance leftward, causing a rightward shift in attentional bias. We tested these claims using low-frequency offline transcranial magnetic stimulation (TMS) to transiently inhibit activity in the right angular gyrus/intra-parietal sulcus, followed by a visual detection task to assess changes in attentional bias, and functional magnetic resonance imaging (fMRI) to test for the predicted leftward shift in brain activity. The task required participants to covertly monitor both hemifields to detect and report the location of upcoming transient visual targets that appeared on the left, right or bilaterally. In the behavioural experiment, participants exhibited a leftward attentional bias ('pseudoneglect') at baseline, which was abolished by TMS. In the fMRI experiment, participants activated an expected network of visual, parietal and frontal cortex bilaterally during the period of covert bilateral attention. TMS shifted the relative hemispheric balance of parietal activity from right to left. The consistent direction of TMS-induced behavioural and functional change indicates a causal role for parietal inter-hemispheric balance in distributing visual attention across space.

1. Introduction

Following injury to right parietal cortex, patients often exhibit visual attentional dysfunction, such as neglect of stimuli in left space. In a related syndrome, extinction, processing of left stimuli is intact, but if presented simultaneously with a stimulus on the right, the stimulus on the right is detected while that on the left is 'extinguished' from awareness. Theoretical models of the pathophysiology of neglect and extinction emphasise the critical role of relative hemispheric dominance and inter-hemispheric competition in controlling the allocation of attention across space (Cohen et al., 1994; Heilman and Van Den Abell, 1980; Kinsbourne, 1977; Mesulam, 1981). The inter-hemispheric competition model posits that the left and right parietal cortices compete to direct attention towards contralateral hemispace, with each hemisphere exerting an inhibitory influence over the other. In a healthy brain, these competing attentional vectors are thought to be broadly counterbalanced, enabling attention to be distributed across both hemifields. However, correlative evidence from brain imaging in healthy volunteers suggests that the right inferior parietal lobe is dominant over the left during bilateral attention (Cicek et al., 2007), consistent with the greater severity of attentional impairments after right than left injury (Weintraub and Mesulam, 1987). Right parietal damage both directly weakens leftward attention, and indirectly, via transcallosal disinhibition, leads to hyper-activation of left parietal cortex, consequently exacerbating a rightward attentional bias. Thus, disrupted parietal inter-hemispheric balance is thought to deviate attention rightward, resulting in a competitive advantage for right hemifield stimuli during tasks that require bilateral attention (de Haan et al., 2012).

Brain imaging and brain stimulation studies have confirmed a role for disrupted inter-parietal hemispheric balance in

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contributing to neglect/extinction in the damaged brain (Corbetta et al., 2005; Corbetta and Shulman, 2002; Koch et al., 2008). However, these models of pathology also make claims about normal function: specifically, that it is the relative balance of activity between left and right parietal cortex that causally mediates bilateral spatial attention. Brain imaging studies have provided confirmatory correlative evidence that participants' behavioural bias between left and right space relates to measures of functional lateralization within attention structures (Benwell et al., 2014; Szczepanski and Kastner, 2013; Thiebaut de Schotten et al., 2011). Causal evidence has come from studies using non-invasive transcranial magnetic stimulation (TMS) to transiently perturb function in parietal cortex. Based on the observed pattern of TMS-induced behavioural interference, inferences have been made about the presumed nature of functional interactions between left and right parietal cortex.

The first two TMS studies of this kind used a visual detection task, designed to mimic clinical confrontation testing of extinction, combined with online high-frequency (Pascual-Leone et al., 1994) or offline low-frequency TMS (Hilgetag et al., 2001). Participants had to monitor both hemifields simultaneously to detect upcoming transient targets, which appeared either on the left, right or bilaterally. In both studies, right parietal TMS impaired detection performance on bilateral trials. In Hilgetag et al.'s study, behaviour was assessed before and after 10 min of 1 Hz TMS applied at rest. The key finding was that right parietal TMS induced a rightward shift in the spatial distribution of participants' errors on bilateral trials. That is, on trials in which participants failed to detect both targets, after TMS they were more likely to detect only the target on the right and omit that on the left, similar to clinical extinction. Subsequent behavioural TMS studies have replicated the finding that right parietal interference impairs detection of left stimuli on bilateral trials (Dambeck et al., 2006; Duecker and Sack, 2014; Meister, et al., 2006). However, the functional basis of impaired performance on bilateral trials is unclear, since an attention deficit for left space would itself compromise bilateral trials, which are the most attentionally demanding and therefore the most sensitive trial type. Hence, existing TMS evidence for a specific causal role of parietal inter-hemispheric balance in mediating bilateral attention currently relies on reverse inference from behavioural impairments and is therefore weak.

Rather than inferring function from behaviour, we combined TMS with fMRI to test directly the hypothesis that normal bilateral attentional function depends on the balance of activity between left and right parietal cortex. We used a visual target detection task previously used to simulate extinction using TMS in the healthy brain (Hilgetag et al., 2001). The aim was to use a task in the MRI scanner that would provide a sensitive means of detecting changes in the balance of parietal inter-hemispheric competition caused by TMS, even if any behavioural effects are likely to be subtle or short-lived.

We targeted stimulation at the caudal part of the angular gyrus (ANG) at the junction with the intra-parietal sulcus (IPS). We therefore refer to the TMS protocol as targeting right ANG/IPS. Stimulation was applied to the right hemisphere, given the dominance of right parietal cortex over left in extinction and neglect (Becker and Karnath, 2007; Cicek et al., 2007), and since previous TMS studies have implicated this region in attention (Ashbridge et al., 1997; Rushworth et al., 2001) and shown that stimulation at this site can induce extinction-like behaviour in healthy individuals.

First, we functionally localised a region of right posterior parietal cortex in each individual at which online high frequency repetitive TMS (10 Hz, 500 ms) disrupted attentional performance (Ashbridge et al., 1997). Anatomical mapping confirmed that this 'hotspot' was located in the caudal part of the right ANG at the junction with the IPS. In a subset of participants, we then confirmed that offline low frequency TMS (1 Hz, 15 min) to that brain region induced extinction-like behaviour in an orthogonal visual detection task. Whereas TMS did not change detection accuracy, the spatial distribution of errors on bilateral trials was shifted from left to right, simulating clinical visual extinction and replicating the key finding of Hilgetag et al. (2001). We then conducted the main fMRI experiment, in which participants performed the same visual detection task, once before and after 1 Hz TMS was applied to transiently inhibit function of the right ANG/IPS. Given the behavioural finding that this stimulation protocol shifted attentional bias from left to right, we analysed the functional imaging data to test the hypothesis that right ANG/IPS TMS would shift the parietal inter-hemispheric balance from right to left.

2. Methods

2.1. Participants

Five right-handed individuals participated in the behavioural TMS experiment (4 male, mean age=23.8 years, SD=4.7). Twelve right-handed individuals participated in the main TMS/fMRI experiment (4 male, mean age=25.9 years, SD=3.5), four of whom also underwent the behavioural TMS experiment. All participants gave written informed consent as approved by the Central Office for Research Ethics Committee (COREC reference number: 05/Q1606/96). All participants had normal or corrected-to-normal vision and indicated no family history of psychiatric or neurological disease. No participant reported any side effect from the experimental procedure.

2.2. TMS functional localisation of right posterior parietal cortex

All participants in both experiments first underwent a 2-h functional localizer session to determine the anatomical target for TMS in each individual. To identify the sub-region of right angular gyrus/intra-parietal sulcus (rANG/IPS) at which stimulation would disrupt attentional function, participants underwent an established mapping protocol previously shown to identify parietal regions functionally involved in the allocation of visual attention (Ashbridge et al., 1997; Rushworth et al., 2001). That location was then targeted for TMS in the main experiments.

Each trial of the functional localisation procedure started with an alerting tone and a white fixation spot (500 ms) at a random location on the screen, followed by the search array (750 ms), composed of red and green diagonal lines on a black background (Fig. 1A). The target was a red line oriented at 45°, surrounded by two kinds of distracters – green lines oriented at 45°, and red lines oriented at 135°. The target was present on half of trials. Participants were instructed to respond on each trial with a right index finger button press if they detected the target and a right middle finger button press if not. The inter-trial interval lasted until participants responded or up until 4 s maximum. The visual search task was run on a computer with a Windows 98 operating system (75 Hz refresh rate 1024×768 resolution) triggered by Turbo Pascal (Version 7.0, Borland International, Inc).

Each participant first performed 10 practice task blocks (10 trials per block), the last 5 of which were performed with sham TMS (coil placed on the head but oriented away), in order to habituate participants to the somatosensory and acoustic artefacts of the subsequent TMS procedure. Earplugs were worn throughout. Participants then performed blocks of the search task, during which a train of high frequency TMS (10 Hz, 500 ms, 65% maximum stimulator output, 70 mm coil) was applied time-locked to search array onset. TMS blocks alternated with baseline blocks, in